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Efficacy of temazepam in frequent users: a series of N-of-1 trials

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Background. Benzodiazepines are frequently prescribed for sleep disturbances. However, benzodiazepines are associated with side effects, and may be ineffective when used for a prolonged period of time.

Objectives. To investigate for individual patients whether placebo was as effective as temazepam, or whether 10 mg was as effective as 20 mg temazepam, and whether these results influenced their future temazepam use.

Methods. A series of randomized double-blind N-of-1 trials were conducted in general practices in The Netherlands for patients who were using temazepam regularly. Each patient received five pairs of treatments consisting of one week of temazepam (10 or 20 mg) and one week of the control intervention (placebo or 10 mg temazepam). Per pair, the sequence of treatments was randomized. Main outcome measures were: time to fall asleep, and the individual main complaint.

Results. Twelve out of 15 patients completed their trial. In three patients there was no difference, in five a large difference, and in four a small difference in favour of temazepam. At follow-up, seven patients had stopped or reduced their temazepam use.

Conclusion. The results regarding the efficacy of temazepam varied across patients. N-of-1 trials seem to be valuable in patients who are motivated to stop or reduce their temazepam use. They clearly demonstrate the efficacy of temazepam, and may give patients additional confidence to discontinue regular hypnotic use. The value of N-of-1 trials for patients who are less motivated is unclear, as the size of treatment effect does not seem to influence future hypnotic use.

Keywords. Benzodiazepines, hypnotics and sedatives, placebos, randomized controlled trials, temazepam.

Introduction

Benzodiazepines are frequently prescribed for sleep disturbances.[1] In 1998, the annual prevalence of benzodiazepine use was estimated at 12.2% in The Netherlands. At least one third of all users were long-term users.[2] However, there is considerable doubt about whether benzodiazepines are still effective when used for a prolonged period of time.[3–5] Additionally, use of benzodiazepines is associated with adverse cognitive effects and an increased risk of motor vehicle accidents, falls and fractures, especially among the elderly.[6–8] Furthermore, benzodiazepines may interact with other medication, such as antidepressants and antiepileptic drugs, resulting in an intensified hypnotic effect.[9] Therefore, in practice guidelines for the management of insomnia it is recommended to prevent or stop long-term use of benzodiazepines.[3,5]

However, attempts made by GPs and their patients to stop long-term use of benzodiazepines are often unsuccessful. Success rates varying from 13% to 59% have been reported.[10–15] The success of such an attempt may be influenced by multiple factors, such as psychological and social factors, dependence on the hypnotic,

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the coaching given by the GP, and variation in the effectiveness of the hypnotic across individuals. But probably the most important obstacle for successful stopping is the awareness of the patient of the abstinence of his or her daily dose of benzodiazepines. N-of-1 trials may provide more insight into the question whether the use of hypnotics can be successfully reduced in individual patients without loss of quality and quantity of sleep. Because in N-of-1 trials both the patient and the GP are blinded for the sequence of treatments, the potential influence of expectations with regard to the effectiveness of the hypnotic is precluded.

N-of-1 trials are carried out with one patient. The patient is his or her own control, and receives alternately the intervention treatment and the control treatment. The sequence of treatments is randomized.[16] N-of-1 trials may help a GP to decide on a treatment policy when there is doubt regarding the effectiveness of medication for an individual patient. N-of-1 trials are especially useful in patients with chronic conditions, and for interventions that have a rapid onset and stop acting soon after discontinuation.[16] Several N-of-1 trials have been carried out and their feasibility in clinical practice seems to be promising.[17–19] Since the purpose of N-of-1 trials is to evaluate the effects of treatments for each individual patient (and not to estimate the average effect for a larger population), the size of a series of N-of-1 trials is of minor importance. Nevertheless, a series of N-of-1 trials will be able to demonstrate the potential variation in outcome across individuals.

The first objective of this study was to investigate for individual patients in general practice whether placebo was as effective as temazepam (10 or 20 mg), or, in some patients, whether 10 mg temazepam was as effective as 20 mg temazepam. The second objective was to investigate whether presenting the personal results of the N-of-1 trial to each individual patient influenced their future use of temazepam.

Methods

Patient selection

Nine GPs from six different towns in The Netherlands participated in the study. Between April and November 2001, they were asked to select patients from their medical records who met the following criteria: regular use of 10 mg or 20 mg temazepam as a hypnotic for at least 4 nights a week during the past 2 months; at least 18 years of age; and no contra-indications for benzodiazepines. Additionally, the patients had to be able to fill in a questionnaire in Dutch and they had to be able to visit the practice.

Design

The selected patients received information about the study, and written informed consent was obtained. The study comprised of a series of N-of-1 trials with a duration of ten weeks. Before the start of their trial, patients were asked about their motivation to participate. To standardize the knowledge on sleep hygiene for all patients, written recommendations for sleep hygiene[3] were given to and discussed with the patient by the GP before the patients received any trial medication. During the study, each patient received five pairs of treatments. Each pair consisted of a one-week period of treatment A and a one-week period of treatment B (Fig. 1). A patient taking 10 mg temazepam before the start of the study received placebo (treatment A) versus 10 mg temazepam (treatment B) during the study; a patient taking 20 mg temazepam before the start of the study received either placebo or 10 mg temazepam (treatment A) versus 20 mg temazepam (treatment B) during the study, depending on the patient's willingness to either reduce the dosage or to stop completely. Per pair of treatments, the sequence of the two treatments was randomized.

The random sequence was prepared in advance by the hospital pharmacist for each patient separately. The patient, the GP and the investigator were blinded for the sequence of treatments. To ensure blinding, identical tablets with regard to colour, smell and taste were used as placebo. If 10 mg temazepam was compared to 20 mg temazepam, additional placebo tablets were given in the 10 mg temazepam treatment periods, so that the patient received 2 tablets each night in all treatment periods. Patients were not instructed to take the medication daily, but every night they decided for themselves whether or not to take the tablets. The patients received the tablets in special boxes, in which each section was coded with a date and contained the tablets for that date. The patients were instructed to leave the tablets they did not take in the boxes. In addition, the patients were asked to indicate each day in a diary whether or not they had taken any hypnotics. The study was approved by the Ethics Review Board of the VU University Medical Center.

Outcome assessment

Outcomes were assessed by means of daily diaries. The primary outcome measures were:

(1) the individual main outcome for which the patient could select among the following outcomes: time to fall asleep (minutes); the patient's perception of the night's sleep (total sleep time sufficient or not); the total sleep time (hours); the number of times awake during the night; the duration of the longest period awake during the night (minutes); and the number of complaints in the daytime (selected from a set of 11, which could indicate withdrawal symptoms or side effects); and

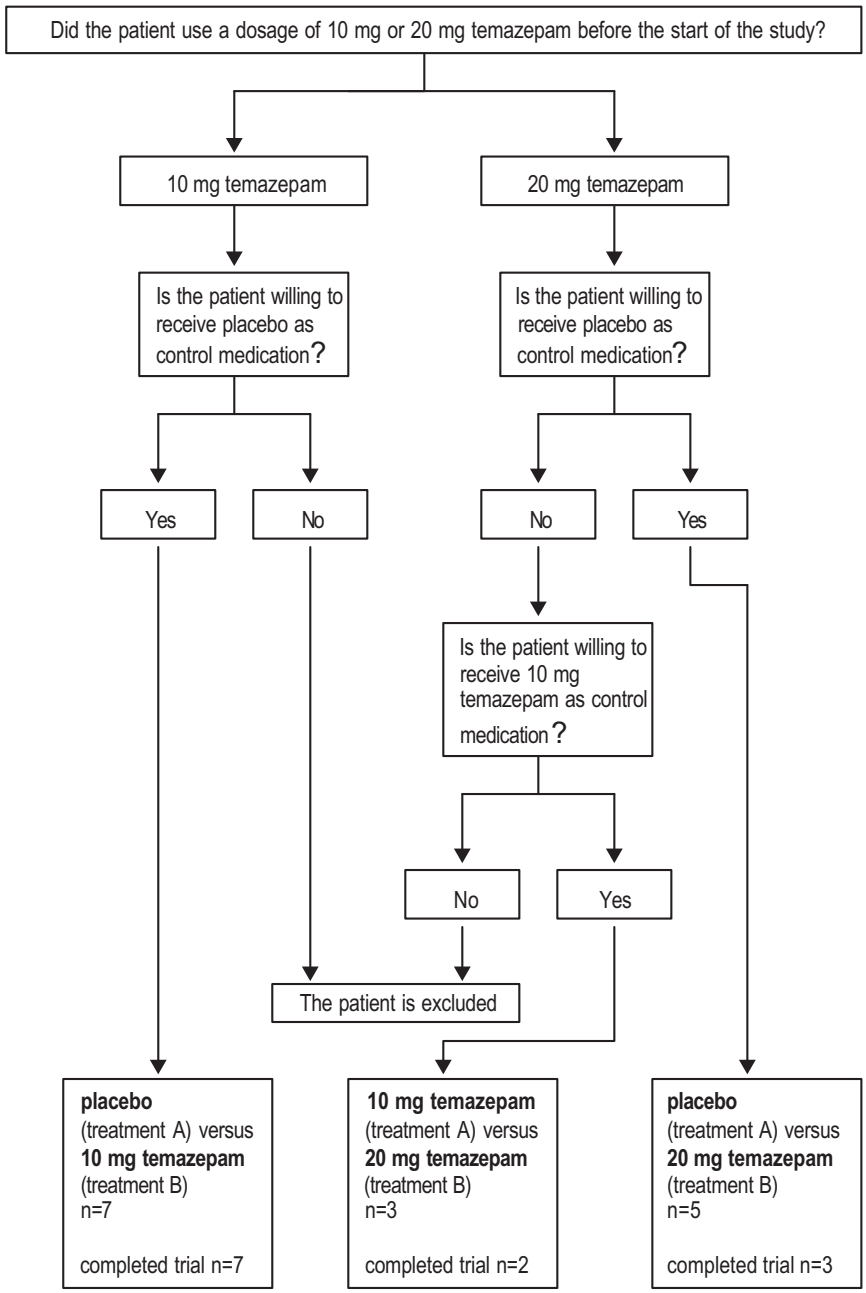

FIGURE 1 *Flow diagram to determine the trial medication per individual*

(2) independent of the individual main outcome, the time to fall asleep (minutes).

All other outcome measures mentioned above were considered as secondary outcome measures for each individual patient. Furthermore, information was collected on co-medication, alcohol intake and afternoon naps. After analysis, plots of their scores on primary and secondary outcome measures were shown to the patients and discussed with them. Three months later the patients were contacted by telephone and asked how many times, and in which dosage, they had taken temazepam during the previous 2 weeks.

Analysis

Since N-of-1 trials were conducted, all outcome measures were analysed for each patient separately. Because of the non-normal distribution of the data, median scores were calculated for all continuous outcomes for each treatment period (Fig. 2). Furthermore, for each treatment period percentages were calculated for the number of nights with a sufficient total sleep time and for the number of days with at least one complaint in the daytime. So-called 'bad' nights were defined as nights in which the time to fall asleep was >60 minutes, or in which the total sleep time was $\leqslant 5$ hours. The percentage of 'bad' nights was calculated for each treatment period.

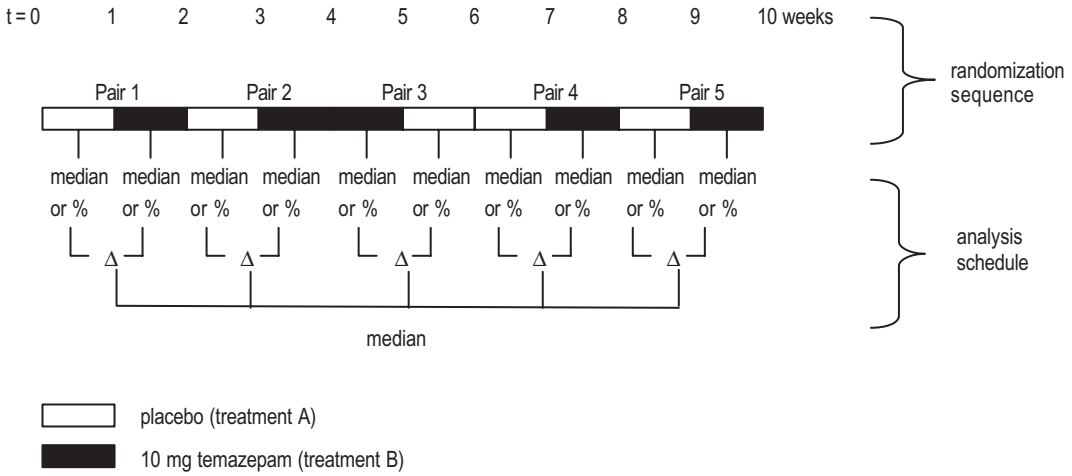

FIGURE 2 *Example of randomization sequence for one patient comparing placebo (treatment A) and 10 mg temazepam (treatment B), and analysis schedule*

Finally, differences in the scores between the compared treatments were calculated (Fig. 2).

A priori, cut off points were defined for the primary outcome measures. A median difference in the time to fall asleep, the total sleep time, or the longest period awake during the night, of at least 30 minutes in favour of temazepam was considered to be a large effect; 5 to 30 minutes a small effect; and <5 minutes no effect of temazepam. For differences in the number of times awake during the night and the number of complaints in the daytime the cut off points for large, small and no effect of temazepam were >1, between 0 and 1, and 0, respectively. Finally, the cut off points for the number of nights with sufficient sleep were a difference of ⩾29% (2 nights in a week), between 0% and 29%, and 0%, respectively for large, small, and no effect of temazepam.

All analyses were carried out according to the intention-to-treat principle. For patients who took less than 75% of the trial medication, an alternative analysis was carried out, including only those days on which the trial medication or additional benzodiazepines had been taken (on-treatment analysis).

Assessment of the plots of the primary and secondary outcome measures showed that there were no carry-over effects, i.e. there were no consistently better results in the first nights (compared to the latter nights) of a control intervention period following a period of (highest dose of) temazepam use or vice versa. Therefore, the results of all 7 days of each treatment period were entered in the analysis.

Results

Subjects

Fifteen patients were selected for participation: ten women and five men (Table 1). Their age ranged between 45 and 78 years (median 62 years). Before the start of the study, seven patients were taking 10 mg temazepam and eight were taking 20 mg temazepam. Of the eight patients who were taking 20 mg temazepam, five received placebo versus 20 mg temazepam, and three received 10 mg temazepam versus 20 mg temazepam during the study.

Three patients (numbers 13, 14 and 15) did not complete the study: one because of nausea after a period of 20 mg temazepam (patient no. 14 after a few days), and two because of insomnia (no. 13 after a few days, after a period of the lowest dose of temazepam; no. 15 after 5 weeks, after a period of 20 mg temazepam). Patient no. 15 took additional benzodiazepines during the last 12 days before she stopped the trial. All three patients took 20 mg temazepam before the start of the study.

Efficacy of temazepam

Twelve patients completed their 10-week trial period. Before the patients were informed about the results of their N-of-1 trial, they were asked whether they had any idea when they had received the (highest dose of) temazepam. Blinding turned out to be successful: none of the twelve patients had noticed that they had taken temazepam as well as the control treatment for periods of one week.

For all patients, there were no or minor differences for co-medication, alcohol intake and the number of afternoon naps between temazepam and the control intervention. The results of the N-of-1 trials regarding the efficacy of temazepam varied across the patients (Table 2). For three patients (nos 1, 2 and 3), the primary outcomes (minutes to fall asleep and the individual main outcome) showed no difference between the two treatments compared. For three other patients (nos 10, 11 and 12), the time to fall asleep was at least 30 minutes in favour of (the highest dose of) temazepam, and the individual main outcome favoured (the highest dose of) temazepam. For five other patients (nos 4, 5, 6, 7 and 8), the primary outcomes favoured temazepam to a lesser extent. Finally, in one patient (patient no. 9), the time to

TABLE 1 *Patient characteristics of 15 participants in N-of-1 trials on the efficacy of temazepam*

Patient no.	Gender (F = female, M = male)	Age	Use of temazepam before start of trial	Total duration of hypnotic use (any type or dose)	Trial medication (mg temazepam)
1	M	47	7 nights/week 20 mg for 5 months	5 months	10 versus 20
2	F	78	7 nights/week 10 mg for 8.5 years	8.5 years	0 versus 10
3	F	48	7 nights/week 20 mg for 11 years	11 years	0 versus 20
4	M	62	6 to 7 nights/week 20 mg for 2 years	6.5 years	0 versus 20
5	M	74	4 to 5 nights/week 10 mg for 8 years	12 years	0 versus 10
6	F	56	7 nights/week 20 mg for 6 years	7 years	0 versus 20
7	F	57	5 nights/week 10 mg for 15 years	15 years	0 versus 10
8	F	45	7 nights/week 10 mg for 8 years	8 years	0 versus 10
9	F	72	7 nights/week 10 mg for 9 years	30 years with intervals	0 versus 10
10	F	73	7 nights/week 20 mg for years	For years	10 versus 20
11	M	70	7 nights/week 10 mg for 6 months	6 months	0 versus 10
12	F	71	4 nights/week 10 mg for 8 years	12 years	0 versus 10
13	F	56	7 nights/week 20 mg for 3 years	3.5 years	10 versus 20
14	M	76	6 nights/week 20 mg for 4 months	4 months	0 versus 20
15	F	53	7 nights/week 20 mg for 2 years	2 years	0 versus 20

TABLE 2 *Results for the 12 patients who completed their N-of-1 trial (negative scores favour (highest dose of) temazepam)*

Patient no.	Trial medication (mg temazepam)	Median difference between treatments (range)				
		Minutes to fall asleep	% nights with sufficient sleep	Minutes slept	No. of times awake during the night	Time awake during the night (minutes)
1	10 versus 20	**0** (−17.5; 35)	0 (−29; 29)	0 (−30; 60)	0 (−1; 1)	0.25 (−12.5; 7.5)
2	0 versus 10	0 (0; 0)	**0** (−14; 0)	−15 (−30; 30)	0 (0; 0)	0 (−5; 0)
3	0 versus 20	**0** (−20; 0)	0 (−40; 17)	−30 (−90; 60)	0 (0; 0)	0 (0; 0)
4	0 versus 20	−15 (−15; 15)	**2** (−14; 29)	0 (0; 60)	0 (−1; 0)	−7.5 (−15; 0)
5	0 versus 10	−12.5 (−125; 0)	−36 (−43; −16)	−45 (−90; −30)	0.5 (−1; 1)	**−2.5** (−32.5; 0)
6	0 versus 20	−5 (−45; 10)	−21 (−57; −7)	−75 (−120; −30)	—[a]	**−15** (−30; −5)
7	0 versus 10	−15 (−30; 30)	**−14** (−29; 36)	−60 (−60; 15)	−0.25 (−1; 0)	−5 (−45; 5)
8	0 versus 10	−5 (−30; 0)	**−26** (−43; 14)	−30 (−60; 45)	0 (−1; 0.5)	−5 (−7.5; 7.5)
9	0 versus 10	−5 (−12.5; 5)	−43 (−43; −12)	−60 (−180; 0)	−1 (−1.5; 0)	**−40** (−205; 20)
10	10 versus 20	**−30** (−45; 10)	9.6 (−14; 29)	0 (−45; 60)	0 (−0.5; 1)	−2.5 (−20; 80)
11	0 versus 10	−30 (−60; 0)	−43 (−46; −12)	−45 (−90; 15)	**−1** (−1; 0.5)	0 (−17.5; 15)
12	0 versus 10	**−45** (−90; 10)	−43 (−55; 19)	−90 (−120; 30)	−0.5 (−1; 1)	−5 (−10; −2.5)

The results of the individual main outcome are presented in bold.
[a] Insufficient information.

fall asleep was only 5 minutes in favour of temazepam, whereas the duration of the longest period awake during the night (the individual main outcome for this patient) was 40 minutes in favour of temazepam. For all patients, there were no or only small differences for the number of complaints in the daytime between temazepam and the control intervention, which indicates no differences with regard to possible withdrawal symptoms or side effects.

For five patients (nos 5, 6, 7, 10 and 12) the percentage of 'bad' nights was at least 29% (2 nights/week) in favour of temazepam for one or both outcomes. For all other patients the percentage of 'bad' nights showed no or only minor differences between the two treatments (<2 night/week).

On-treatment analysis

Ten of the twelve patients who completed the study took at least 94% of the trial medication. The other two patients took less than 75% of the medication (patient no. 2, 60%; patient no. 7, 43%), so on-treatment analysis was carried out. For patient no. 2 the on-treatment analysis showed similar results as the intention-to-treat analysis for the individual main outcome, but the time to fall asleep was 15 minutes in favour of placebo according to the on-treatment analysis. For patient no. 7 the results of both primary outcomes were more strongly in favour of temazepam according to the on-treatment analysis. The time to fall asleep was 49 minutes shorter during

TABLE 3 *Results for the 15 participants in N-of-1 trials: motivation to participate, efficacy of temazepam, intended future use of hypnotics, and hypnotic use three months after presenting the outcomes*

Patient no.	Motivation to participate in N-of-1 trial	Efficacy of temazepam	Intended medication	Medication after 3 months use after trial
1	S	No effect	Reduce dose and freq	As before study
2	P	No effect	Reduce freq	Reduced freq
3	P	No effect	Stop	Stopped
4	S	Small effect	Reduce freq	As before study
5	S	Small effect	As before study	As before study
6	P	Small effect	Reduce freq	Reduced freq
7	P	Large effect (on-treatment analysis)	As before study	As before study
8	P	Small effect	Reduce freq or stop	Reduced freq
9	P	Large effect	Stop	Stopped
10	S	Large effect	Reduce dose and freq	Reduced dose and freq
11	P	Large effect	Stop	Stopped
12	S	Large effect	As before study	As before study
13[a]	P	–	–	–
14[a]	O	–	–	–
15[a]	P	–	–	–

P = Patient motivated to stop or reduce temazepam use; S = for the benefit of science; O = other (asked by the GP's assistant); freq = frequency.
[a] Patient numbers 13, 14 and 15 did not complete their trial.

temazepam use and the percentage of nights with sufficient total sleep time was 30% in favour of temazepam, according to the on-treatment analysis.

Efficacy of temazepam and follow-up

After presenting the results of the primary and secondary outcome measures to the patients, they were asked about their intentions with regard to future temazepam use (Table 3). All three patients for whom the primary outcomes showed no difference between the treatments (nos 1, 2 and 3) intended to stop or reduce the use of temazepam. At three months follow-up one patient (no. 1) again used temazepam as before the study. Three of the four patients who showed a small benefit of temazepam (nos 4, 6 and 8) intended to stop or reduce the use of temazepam, but only two persisted in this intent at three months follow-up. Finally, three of the five patients with large effects of temazepam (nos 9, 10, and 11) had stopped or reduced the use of temazepam at three months follow-up as intended shortly after the trial. In sum, seven of the 12 patients had stopped (3 patients) or reduced (4 patients) temazepam use at follow-up. There seemed to be only a weak association between the efficacy of temazepam and the intentions regarding future temazepam use, and no association between the efficacy of temazepam and the actual hypnotic use at follow-up.

Motivation to participate

Nine of all 15 patients indicated at baseline participated in the study because they wanted to stop or reduce their use of temazepam. Five patients participated for the benefit of science and one because "he was asked to participate by the GP's assistant" (Table 3). This last patient (no. 14) did not complete his trial. Of the nine patients who were motivated to reduce their temazepam use, two did not complete their trial (nos 13 and 15), six stopped or reduced the use of temazepam at three months follow-up (nos 2, 3, 6, 8, 9, and 11), and only one used temazepam as before the study (no. 7). Among the five patients who participated to benefit science, one patient had reduced the use of temazepam (no. 10) and four used temazepam as before the study (nos 1, 4, 5, and 12) at the three months follow-up.

Discussion

In a series of randomized, blinded N-of-1 trials we investigated the efficacy of temazepam in frequent users of hypnotics. Twelve of the fifteen patients (80%) completed the 10-week trial period. The results among the 12 completers varied from no difference to large differences in favour of (the highest dose of) temazepam. The results did not seem to be associated with the dosage of temazepam used during the trial. For example, among the three patients who experienced no effect of temazepam, one patient received placebo versus 10 mg temazepam, another 10 mg versus 20 mg temazepam, and the third placebo versus 20 mg temazepam.

Large-scale trials have shown that attempts to stop temazepam use are only successful in 13 to 59% of patients.[10–15] There is little evidence regarding the factors that may predict which patients can or cannot successfully reduce the use of temazepam. Age under 65[10] has been reported to be associated with a successful attempt, but this evidence is not consistent across studies. In our series age did not seem to influence outcomes.

Cormack *et al*. demonstrated that a relatively low consumption of benzodiazepines[11] was associated with a successful attempt. However, in our series, none of the three patients taking temazepam five or less times a week at baseline, intended to stop or reduce temazepam use after the trial. Due to the less frequent use of temazepam compared to the other patients in the study, it may be harder to achieve a reduction in the frequency of temazepam intake.

N-of-1 trials demonstrate the efficacy of temazepam in each individual patient, and may thereby provide a good indication of the possibility to reduce hypnotic use. However, in our series, the actual results of the trials did not seem to be a strong predictor of future use of temazepam. Patients decided either to stop, reduce, or continue the use of hypnotics regardless of the effect of temazepam shown by their trial. While the influence of treatment effect appeared to be limited, the motivation of the patients to participate in the study seemed to be of greater importance. Six of the seven patients who completed their trial and had indicated that they participated in the study because they wanted to reduce temazepam intake, successfully reduced temazepam use during follow-up. In contrast, out of the five completers who participated for the benefit of science only one reduced the intake of hypnotics.

The potential influence of motivation to change behaviour has been demonstrated in other research. In an intervention study among 72 long-term benzodiazepine users Morrison[12] found that it was significantly more likely that the patient would stop taking the drug if they originally wished to do so.

The question arises whether the patients with a (strong) internal motivation needed the N-of-1 trial to change hypnotic intake. In our opinion, the participation in an N-of-1 trial may strengthen the intent to change hypnotic use. Eight of the nine patients who intended to reduce temazepam intake stated that the N-of-1 trial had contributed to this decision. By participating in a trial the patients are given more attention to their use of temazepam and become more aware of their frequent hypnotic use. This attention itself may be of more importance than the results of the individual trials to stimulate the patients to stop or reduce the temazepam intake. In addition, for patients who are willing to reduce temazepam intake, but are somewhat afraid to do so, an N-of-1 trial may be more effective than an unblinded attempt to reduce intake. The awareness of abstinence of temazepam may cause insomnia, which may negatively influence the success of the attempt. The fact that the blinded design of an N-of-1 trial may facilitate the attempt to reduce drug use is illustrated by a statement made by patient no. 3:

> "For a long period of time [before the study], I wanted to stop, but I was uncertain whether I could hang on. Because of the project I had to persist. All the time during the trial, I slept reasonably well, and it made no difference what I took [temazepam or placebo]. Therefore I stopped [taking sleep medication]."

At follow-up, seven of the 12 patients who completed the trial, had stopped or reduced their temazepam intake. Therefore, double-blinded N-of-1 trials may be viewed as an instrument for GPs to reduce the unnecessary temazepam use of their patients, especially for those who are willing but somewhat afraid to do so.

Blinding of patients was successful, unexpectedly even for patients in whom temazepam favoured placebo (or lower dosage of temazepam) to a larger extent. This may be explained by the fact that quality and quantity of sleep varied across nights regardless of the type of treatment, meaning that patients were not always sleeping well when taking temazepam, and not always sleeping badly when taking the control intervention. The latter can also be concluded from the range in outcomes within the patients presented in Table 2. Furthermore, for all patients, there were no or only small differences for the number of complaints in the daytime (possible withdrawal symptoms or side effects) between temazepam and the control intervention, which helped to ensure blinding.

The drop-out rate in our study was relatively low (3 of the 15 patients). To prevent drop-out due to the length of the trial period, we wanted to keep the trial period as short as possible. However, this also implies that the power, which depends on the number of treatment pairs, is limited. These aspects should be weighed against each other when designing an N-of-1 trial.[20] The power of a study is also related to the type of significance testing. Although significance testing may be possible in N-of-1 trials, our data were not suitable for quantitative analysis, partly due to the non-normal distribution of the data. More importantly, we did not investigate whether one treatment was better than the other, but whether one treatment was equally effective as the other. In other words, the N-of-1 trials were equivalence trials, rather than superiority trials. This implies that conventional significance testing could not be used for analysis.[21] This topic was also addressed in a reaction to a series of N-of-1 trials by March *et al*., in which it was pointed out that failure to find a significant difference in favour of a treatment may not be regarded as proof of equivalence.[22,23] As a consequence, we decided to formulate *a priori* cut off points, which were very helpful to determine the magnitude of treatment effect, and to identify the variation in efficacy of temazepam across patients.

In conclusion, N-of-1 trials provide clear evidence about the impact of temazepam on the quality and quantity of sleep in individual frequent users of hypnotics. In patients who are motivated to stop or reduce their temazepam intake, participation in the trial may give additional confidence to successfully reduce temazepam use. The value of N-of-1 trials for patients who are less motivated is

unclear, as the size of treatment effect does not seem to influence future use of hypnotics. For less motivated patients experiencing small or no effect of temazepam, additional coaching by the GP, and education about the potential risks and disadvantages of long-term or frequent use of hypnotics may offer possibilities to reduce their unnecessary temazepam use. For patients experiencing large benefits and no potential disadvantages of temazepam, continued use of temazepam could be justified. Our study demonstrated that there is a realistic potential that N-of-1 trials are helpful in reducing benzodiazepine use in primary care. The next step could be to study, in a randomized clinical trial, whether N-of-1 trials are more successful than other interventions in primary care to reduce unnecessary temazepam use.[24] Finally, the design and execution of N-of-1 trials is time-consuming. Therefore, also the applicability of N-of-1 trials in general practice needs further study, in order to assess the possibilities of implementing these trials in daily practice.

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Declaration

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Conflicts of interest: none.

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